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PATENT TRADEMARK OFFICE

Docket No: 2094/1E286-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Jeffrey M. LINNEN and Kevin M. GORMAN

Serial No.: 09/493,353 Art Unit: 1655

Filed: January 28, 2000 Examiner: J. Goldberg

For: OLIGONUCLEOTIDE PRIMERS FOR EFFICIENT DETECTION OF HEPATITIS C VIRUS (HCV) AND METHODS OF USE THEREOF

RESPONSE TO OFFICE ACTION AND AMENDMENT UNDER 37 C.F.R. § 1.111

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

In response to the Office Action mailed on April 19, 2001 for this application and in accordance with Rule 111 of the Rules of Practice, please enter the following amendments and consider the accompanying remarks. The amendments are made pursuant to the requirements of Rule 121 in the Rules of Practice. Accordingly, Applicants are submitting herewith: (1) a copy of the

amended claims marked up, as required under 37 C.F.R. § 121(c)(ii), to show all changes relative to the previous version of each claim and attached hereto at Exhibit Tab A. Applicants also submit herewith, for the Examiner's consideration along with the below remarks:

(2) a copy of the decision by the U.S. Court of Appeals for the Federal Circuit (the "Federal Circuit") for the case of *In re Deuel*, 34 USPQ2d 1240 (Fed. Cir. 1995), attached hereto at Exhibit Tab B; and

(3) a copy of the Federal Circuit's decision for the case of *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), attached hereto at Exhibit Tab C.

A Petition for Extension of Time is also submitted herewith, accompanied by the appropriate fee and requesting that the time period for responding to the Office Action be extended for **one** month, from **July 19, 2001** up to and including **Monday, August 20, 2001**. It is believed that no other fees are required for these submissions. However, should the U.S. Patent and Trademark Office determine that any additional fee is due or that a refund is owed for this application, the Commissioner is authorized and requested to charge any fee(s) due and/or credit any refund(s) owed to Deposit Account No. 04-0100.

Please amend the application as follows:

IN THE CLAIMS:

Amend claims 13 and 42 as indicated on the attached Exhibit A so that the claims reads as follows:

13. (Amended) A method as defined in claim 12, wherein said probes comprise a member selected from the group consisting of:

(a) 5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13> and

C1

(b) 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12> when said forward primer is (C131F25) or (C143F26); and

wherein said probes comprise

(c) 5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11> when said forward primer is (C69F28).

42. (Twice amended) An oligonucleotide probe selected from the group consisting of:

5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11>;

C2

5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12>;

5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13>;

5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14>; and

C2 5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

REMARKS

At the outset, Applicants thank Examiners Jeanine Goldberg and Lisa Arthur for the courtesies extended during the telephonic interview with Applicants' undersigned representative on Wednesday, July 25, 2001. The remarks presented here reflect the content of that interview.

Claims 1-64 are pending in this application. Claim 13 has been amended to correct a typographical error discovered by Applicants upon review of the pending claims. In particular, claim 13 has been amended to properly depend from claim 12 rather than from claim 10. Claim 42 has also been amended, to more particularly recite that the claimed oligonucleotides are ones selected from those specifically recited in that claim. These amendments do not contain new matter and claims 1-64 will remain pending upon the amendments' entry. Entry and consideration of these amendments and remarks are therefore respectfully requested.

THE REJECTIONS FOR ANTICIPATION UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

The Examiner has maintained the previous rejections of claim 42 under 35 U.S.C. § 102(b) as anticipated by both the reference of Han *et al.*, "Characterization of the terminal regions of hepatitis C viral RNA: Identification of

conserved sequences in the 5' untranslated region and poly(A) tails at the 3' end" *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88:1711-1715 (hereinafter referred to as "Han"), and the reference of Kolykhalov *et al.*, "Identification of a Highly Conserved Sequence Element at the 3' Terminus of Hepatitis C Virus Genome RNA" *J. Virology* 1996, 70(6):3363-3371 (hereinafter referred to as "Kolykhalov").

Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. See, M.P.E.P. § 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Every element of the claimed invention must be literally present, arranged as in the claim. *Perkin Elmer Corp.* 732 F.2d 888, 894, 221 USPQ 669, 673.

In the present instance, the relevant inquiry is whether a single reference (*i.e.*, either Han or Kolykhalov) discloses an oligonucleotide probe or primer having a particular nucleotide sequence recited in the pending claim. According to the Office Action, the Han and Kolykhalov references teach genomic HCV sequences from which the presently claimed oligonucleotide sequences are derived. The genomic HCV sequences taught by these references therefore contain, as subsequences, particular oligonucleotide sequences recited in claim 42. Although claim 42 actually recites an "*oligonucleotide probe*," the Examiner argues

that the recitation of "oligonucleotide" in the claim does not provide any structural or length limitations.

In response, Applicants respectfully submit that the term "*oligonucleotide*" has a meaning well recognized in the art as referring to short nucleic acid sequences, *e.g.*, of about 20-25 nucleotides in length. The term is, therefore, a limitation that excludes full length genomic sequences such as the ones taught by Han and Kolykhalov. Claim 42 has been amended to more particularly point out this intrinsic limitation. In particular, claim 42, as amended, particularly recites an oligonucleotide probe selected from one of the specific oligonucleotides recited in that claim.

For the above reasons, Applicants submit that the rejections under 35 U.S.C. § 102 have been obviated, and respectfully request that the rejections be withdrawn.

THE REJECTIONS FOR OBVIOUSNESS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

The Examiner has maintained the following rejections for obviousness:

(1) Claims 1, 3-13 and 40-42 stand rejected as obvious over the Han reference (*supra*);

(2) Claims 43, 45, 47, 49-50, 54, 56, 58 and 60-61 stand rejected as obvious over Han (*supra*) in further view of Ahern, "Biochemical

Reagent Kits Offer Scientists Good Return on Investment", *The Scientist* 1995, 9(15):20 (hereinafter referred to as "Ahern");[1]

(3) Claims 14, 16-26 and 40-42 stand rejected as obvious over the Kolykhalov reference (*supra*);

(4) Claims 51-53 and 62-64 stand rejected as obvious over Kolykhalov (*supra*) in further view of Ahern (*supra*);

(5) Claims 14, 16-26 and 40-42 stand rejected as obvious over U.S. Patent No. 5,837,463 which issued on November 17, 1998 to Tanaka *et al.* (hereinafter referred to as "Tanaka") and over Encke *et al.*, "Total Chemical Synthesis of the 3' Untranslated Region of the Hepatitis C Virus with Long Oligodeoxynucleotides", *J. of Virological Methods* 1998, 74:117-121 (hereinafter referred to as "Encke");

(6) Claim 15 stands rejected as being obvious over the Tanak and Encke references (*supra*) further in view of U.S. Patent No. 5,846,704 issued December 8, 1998 to Maertens *et al.* (hereinafter referred to as "Maertens");

(7) Claims 27-39 stand rejected as being obvious over either Maertens or Han in view of either Kolykhalov or Tanaka and Encke; and

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[1] This reference has been cited in the Office Action by the internet web page: www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998.

(8) Claims 44, 46, 48, 55, 57 and 59 stand rejected as being obvious over either Maertens or Han in view of either Kolykhalov or Tanaka and Encke, and in further view of Ahern.

In addition, the Office Action imposes new grounds of rejection. Specifically, the pending claims have also been rejected for obviousness as follows:

(9) Claims 1-2, 4-6, 9-12, 43, 45, 54 and 56 have been rejected under 35 U.S.C. § 103(a) as being obvious over Maertens (*supra*).

In making the above rejections, the Examiner has noted that the cited references teach either a conserved 3'-UTR of the hepatitis C virus (HCV) genome RNA (see, in particular, the references of Kolykhalov, Tanaka and Encke), a conserved 5'-UTR of the HCV genome RNA (see, in particular, the references of Han and Maertens), and/or the use of primer pairs from these regions to amplify or analyze HCV sequences. The Examiner also argues that certain references (*e.g.*, Maertens) do teach specific oligonucleotide primers that overlap primer sequences recited in the pending claims. However, the Examiner has acknowledged, in the Office Action, that none of the cited references explicitly teaches the actual oligonucleotides of the claimed invention.

Instead, the obviousness rejections appear to be based, at least in part, on the contention that these oligonucleotides are actually structural homologs

of the full length genomic sequences disclosed in the cited art. The Office Action then concludes, citing the court decision of *In re Deuel*,[2] that the oligonucleotides would be *prima facie* obvious to a person skilled in the art. In response to these arguments, Applicants respectfully submit that the present Office Action fails to establish a *prima facie* case for obviousness under the standards that have been established by the United States Court of Appeals for the Federal Circuit (Federal Circuit) and are set forth in the Manual for Patent Examining Procedure (M.P.E.P.).

The legal standard for obviousness under 35 U.S.C. § 103:

Three basic criteria must be met to establish a *prima facie* case for obviousness under 35 U.S.C. § 103(a). First, there must be a concrete suggestion or motivation to modify what is taught in a reference or to combine its teachings with other references. Second, there must have been a reasonable expectation that the modifications or combination would succeed. Finally, the combined or modified prior art must actually teach all of the claimed limitations. The motivation and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. See, M.P.E.P. § 2143, citing *In re Vaeck*, 947 F.2d 488, USPQ2d 1438 (Fed. Cir. 1991). Obviousness can only be established by

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[2] 51 F.3d 1551, 34 USPQ2d 1210 (Fed. Cir. 1995). For the Examiner's convenience, a copy of the *Deuel* decision (from the U.S. Patents Quarterly reporter) is attached hereto, at Exhibit Tab B. Citations to particular pages in that decision are made here with respect to the attached copy.

combining or modifying the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. M.P.E.P. § 2143.01. See, also, *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The mere fact that references may be combined or modified does not render the resulting combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 143 (Fed. Cir. 1990).

Here, therefore, the relevant inquiry is whether a skiled artisan, given knowledge of the HCV 5'-UTR and/or 3'-UTR sequences taught in the above-cited references, would have been motivated to select, from those full length sequences, the particular oligonucleotides recited in the pending claims, and to use those oligonucleotides to amplify and detect HCV nucleic acids in a biological sample. The invention, as a whole, must be apparent to the skilled artisan with a reasonable expectation of success. M.P.E.P. § 2143.02. Thus, the skilled artisan must not only be motivated to select the particular oligonucleotides recited in the pending claims. He or she must also have a reasonable expectation that those sequences will successfully amplify and detect HCV nucleic acids in a biological sample, such as a clinical sample from a patient.

The Deuel decision does not change the requirements for prima facie obviousness under 35 U.S.C. § 103:

The Examiner, in making the obviousness rejections, seems to believe that the particular oligonucleotide sequences of this application are suggested by the prior art because, according to the Office Action, they are structural homologs of full length 5'-UTR or 3'-UTR sequences taught in the cited art. The Examiner supports this proposition by citing *In re Deuel* (*supra*), noting that:

> [n]ormally a *prima* facie case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.[3]

However, the *Deuel* court immediately goes on to note that:

> [i]n all of these cases . . . the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the ***specific*** molecular modifications necessary to achieve the claimed invention.[4]

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[3] *Deuel* (*supra*) at 1214. Cited in the Office Action at pages 6, 11, 16 and 27.

[4] *Ibid* (emphasis added).

Thus, the *Deuel* court's decision does not, in any way, establish an exceptional legal standard for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. Rather, *Deuel* supports the proposition that, for the presently claimed invention to be obvious, a skilled artisan must be motivated, *a priori*, to select the specific oligonucleotides recited in the pending claims. As noted in the present Office Action, however, none of the cited references suggests these particular modifications to either the HCV 3'-UTR or the 5'-UTR. In particular, they do not suggest with any reasonable expectation of success that the particular oligonucleotides recited in the pending claims will amplify or detect HCV in a biological sample.

Obvious "to try" is not the standard for obviousness under 35 U.S.C. § 103:

At best, the references cited in the Office Action might simply motivate a skilled artisan to try various oligonucleotides from the full length 3'-UTR and/or 5'-UTR sequences, with the expectation that he or she might find some oligonucleotides that can be used successfully to reverse transcribe and/or detect HCV RNA in a biological sample. However, this does not establish a *prima facie* case for obviousness under 35 U.S.C. § 103. To better illustrate this point, the

Examiner's attention is directed to the Federal Circuit's decision in *In re O'Farrell*.[5] In *O'Farrell*, the court considered common circumstances where an invention that may have been "obvious to try" nevertheless is not legally obvious under 35 U.S.C. § 103. In particular, the court notes:

> In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.[6]

The *O'Farrell* decision makes it clear that an invention made under such circumstances is not legally obvious under 35 U.S.C. § 103.

The situation here is similar, if not identical, to that described above by the court in *O'Farrell*. In particular, the teachings of the above-cited references might, at best, only motivate a skilled artisan to try different oligonucleotides that are complementary to parts of the 5'- or 3'-UTR sequences taught in those references, to amplify and/or detect HCV in a biological sample. Yet even though certain references may teach that "[a]ny primer which specifically hybridizes to the

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[5] 853 F.2d 984, 7 USPQ2d 1673 (Fed. Cir. 1988). For the Examiner's convenience, a copy of the *O'Farrell* decision (from the U.S. Patents Quarterly reporter) is attached hereto, at Exhibit Tab C. Citations to particular pages in that decision are made here with respect to the attached copy.

[6] *O'Farrell* at 1681 (citations ommitted).

[HCV UTR] can be used",[7] the cited references do not give adequate guidance so that a skilled artisan may determine *which* particular oligonucleotides will specifically hybridize to the 3'-UTR and/or the 5'-UTR and not to other sequences that may be present in the biological sample.

A skilled artisan would therefore need to experiment and try various oligonucleotides that are complementary to the 3'-UTR and/or 5'-UTR, to determine which particular ones hybridize to those HCV sequences with the required specificity. In particular, the skilled artisan would need to identify, by experimentation, particular oligonucleotide sequences that hybridize to those target HCV nucleic acids in a biological sample and with sufficient specificity that they may be used successfully to amplify and/or detect the HCV. The mere fact that a particular oligonucleotide of this application might eventually be identified through such experimentation does not render it legally obvious under 35 U.S.C. § 103, even if such experimentation were routine and not undue. The Federal Circuit's decisions of *Deuel* and *O'Farrell* clearly establish that, for a particular oligonucleotide of this application to be obvious, a skilled artisan must reasonably expect *a priori* that the oligonucleotide will hybridize to the target HCV sequence with sufficient specificity so that it may successfully amplify and/or detect that HCV nucleic acid. The skilled artisan must therefore reasonably expect success

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[7] See, for example, at lines 50-52 in column 2 of Tanaka.

from the particular oligonucleotide without having to engage in any experimentation (routine or otherwise) to identify particular oligonucleotides that would be suitable.

No reasonable expectation of success:

As explained in Applicants' previous amendment, a skilled artisan could not have had, *a priori*, any such reasonable expectation of success. In particular, Applicants respectfully direct the Examiner's attention to Chapter 15.1, "Enzymatic Amplification of DNA by PCR: Standard Procedures and Optimization" from Ausubel *et al.* (Eds.), *Current Protocols in Molecular Biology*, Vol. 3 (John Wiley & Sons, 1998) pages 15.1.1-15.1.15 ("Ausubel").[8] As previously pointed out by Applicants, the Ausubel reference clearly teaches that primer selection is "unpredictable" and "difficult to trouble shoot."[9] While Ausubel may indicate some guidelines to consider when designing primers for a particular assay, these guidelines merely serve to increase the probability that a given primer pair will work. Ausubel further admonishes that primer design (*e.g.*, by computer) "is not foolproof."[10] Thus, even though primer selection may be routine, Ausubel clearly establishes that some experimentation will be necessary to identify which particular

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[8] The Ausubel reference was cited in Applicants' previous Amendment, and is attached thereto at Exhibit Tab C.

[9] See, in particular, the right hand column on page 15.1.7 of Ausubel.

[10] See, specifically, the right hand column on page 15.1.9 of Ausubel.

primers are successful. In short, a skilled artisan cannot reasonably predict *a priori* whether a particular primer pair will hybridize to a target sequence (*e.g.*, in a biological sample) with the requisite specificity.

For the reasons set forth above, Applicants respectfully submit that a *prima facie* case for obviousness has not been established and request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

For the reasons stated above, Applicants believe that the Examiner's rejections of the pending claims have been overcome and that the claims, as amended, are in condition for allowance. Accordingly, the withdrawal of all objections and rejections, and reconsideration of the application are respectfully requested. The Examiner is invited to contact Applicants' undersigned representative at the below indicated telephone number if she believes it may advance prosecution of this application. An allowance is earnestly sought.

Respectfully submitted,

Dated: August 17, 2001

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